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EMETIC MECHANISM IN ACUTE RADIATION SICKNESS

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Technical Report

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

A dose-response relationship was established in normal cats for the evocation of vomiting within 24 h after whole-body exposure to ^{60}Co radiation with doses ranging from 7.5 to 60 Gy delivered at 1.0 Gy/min. Vomiting was recorded oscillographically. Radiation-induced vomiting was elicited unabatedly at the optimal dose of 45 Gy in chronically postremectomized cats. Radioemetic susceptibility was evaluated in normal cats after each of two doses of radiation, from 7.5 to 60 Gy, given on successive days. Occurrence of radioemetic protection against the second irradiation was manifested in direct relation to the magnitude of the first exposure, and complete protection for 24 h resulted after second radiation exposure at the highest dose level. Postremectomized cats were also fully protected against the radioemetic effect of a second exposure at 45 Gy. All normal cats vomited in response to an emetic drug injection during the state of radioemetic refractoriness after the second irradiation at 45 Gy. A neural origin of the

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19. ABSTRACT (Continued)

emetic signal generated by first radiation exposure was examined in postrema-intact cats as follows. Afferent nerve pathways from the abdomen to the vomiting center were interrupted chronically by means of (1) subdiaphragmatic vagotomy and/or (2) high dorsal column spinal cordotomy. Vagotomy alone prolonged the latency of the radio-emetic response, and cordotomy alone ameliorated the vomiting while it eliminated anorexia and malaise. The combination of vagotomy and cordotomy prevented the entire syndrome of acute radiation sickness. It is concluded from these experimental results in cats that: (1) the area postrema does not mediate radiation-induced vomiting; (2) irradiation produces after 24 h a desensitization of radioemetic receptors to re-irradiation which is proportional to the magnitude of initial exposure and which does not involve the area postrema; (3) no rational basis exists for the postulation of a circulating chemical factor released by radiation and presumed to act on the emetic chemoreceptor trigger zone in the area postrema; (4) radiation-induced vomiting is evoked by the activation of vagal and segmental afferent neural pathways arising in the abdomen and leading to the vomiting center in the medulla oblongata.

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SUMMARY

A comparison was made of radioemetic behavior in normal and postremectomized cats. We observed emetic activity objectively by recording intrathoracic pressure signals on an oscillograph over a period of 24 hours following irradiation of the cat. The ^{60}Co radiation dose-emetic response relationship was established in normal cats for selection of the optimal radioemetic dose to be used in postremectomized cats. We then determined that the radioemetic behavior of the lesioned cats was functionally indistinguishable from that of normal cats. Similar findings were obtained in X-irradiated cats We concluded from these results that neither the area postrema (AP) nor a chemogenic activator of the AP is essential for the evocation of radioemesis.

Radioemetic susceptibility was evaluated in cats after each of two doses of ^{60}Co whole-body irradiation given on successive days. We demonstrated that the interposed recovery period on the second day after a single exposure, between prompt and delayed phases of radiation sickness, coincides with the selective development of radioresistance. Radioemetic protection against the second irradiation was observed to be directly related to the magnitude of the first dose of radiation given 24 hours earlier. Vomiting was evoked by drug injection at the time when complete emetic refractoriness was manifested to the second dose of radiation. Postremectomized cats behaved in a manner indistinguishable from normal with respect to the post-irradiation development of radioemetic resistance. We concluded from these results that the protection afforded against radiation sickness by prior irradiation results from selective desensitization of the radioemetic sensory target, and that the AP is not essential for this effect.

A study was made in cats of the afferent neural pathways in the radioemetic reflex arc that bypass the AP. We interrupted segmental centripetal fibers to the dorsal medulla by the simple surgical procedure of sectioning the dorsal column nuclei of the spinal cord. This maneuver by itself considerably ameliorated the radioemetic syndrome and it eliminated the attendant anorexia. The combination of subdiaphragmatic vagotomy with interruption of the dorsal columns resulted in complete protection of chronic cats against acute radiation sickness. We concluded from these results that the radioreceptive target, very likely located in the upper abdomen, is "hardwired" to the vomiting center thereby excluding any involvement of a circulating chemical factor in the etiology of the acute radioemetic syndrome.

PREFACE

The key professional investigators on this project, in alphabetical order, consisted of Herbert L. Borison, Rosaline Borison, Evan B. Douple, Joan R. Johnson and Lawrence E. McCarthy.

The assistance of Emerson Colby, Alexander Filimonov, Tracey Fisk, Mary Goodheart and Robert Richmond is gratefully acknowledged.

The irradiation facilities of the Norris Cotton Cancer Center were supported in part by DHHS, NCI Core Grant CA-23108.

This research was conducted according to the principles enunciated in the "Guide for Animal Facilities and Care" prepared by the National Academy of Sciences--National Research Council.

LIST OF ILLUSTRATIONS

SECTION 1

GENERAL INTRODUCTION

1.1 PHYSIOLOGIC PROCESS OF VOMITING.

1.1.1 Central Control of Vomiting.

Vomiting is a reflex function of the nervous system controlled by the vomiting center in the medulla oblongata of the lower brain stem. The control center was first localized in the medullary reticular formation by Borison and Wang (1949) utilizing stereotaxic technique for electrical stimulation of the brain parenchyma. Up to that time, the vomiting center was thought to be located more superficially in the dorsal vagal nuclei. Modern understanding of the vomiting reflex mechanism is based on the concept developed in the early original work of Borison and Wang (reviewed in 1953) replacing the former prevailing view promoted by Hatcher and Weiss (1923). Accordingly to our newly developed concept, all forms of vomiting are coordinated by the vomiting center responding to activation by nerve impulses. The vomiting center is not directly responsive to chemical emetic stimulation; rather, the detection of chemical stimuli is performed by specialized chemoreceptors from which the emetic reflex signal is conducted to the center through afferent nerve fibers. This is a sharp departure from the belief of Hatcher and Weiss that the vomiting center could be directly activated by emetic chemicals.

The various central contributing elements to the reflex control of vomiting are shown in their approximate spatial relationship within the medulla oblongata in the diagram of figure 1. The primary input source of chemically-induced vomiting is the emetic chemoreceptor trigger zone (CTZ) discovered by Borison and Wang on the surface of the medulla oblongata overlying the dorsal vagal nuclei (Borison and Wang, 1951; Wang and Borison, 1952).

1.1.2 The Area Postrema Embodies the Emetic Chemoreceptor Trigger Zone.

After the chemoreceptor trigger zone was discovered as a functional entity, its morphological embodiment in the area postrema (AP) was identified by Borison and Brizzee (1951). The AP is the most caudal member of the circumventricular organ (CVO) system comprising a group of subependymal vascular proliferations that are distributed on the pial-ependymal margin of the brain and which lack the blood-brain barrier (Borison, 1984). Except for the well established chemosensory function of the AP in vomiting, a more general role of the CVO system remains enigmatic although an uncertain kind of neuroendocrine communication through the cerebrospinal fluid has been suggested (Weindl, 1973).

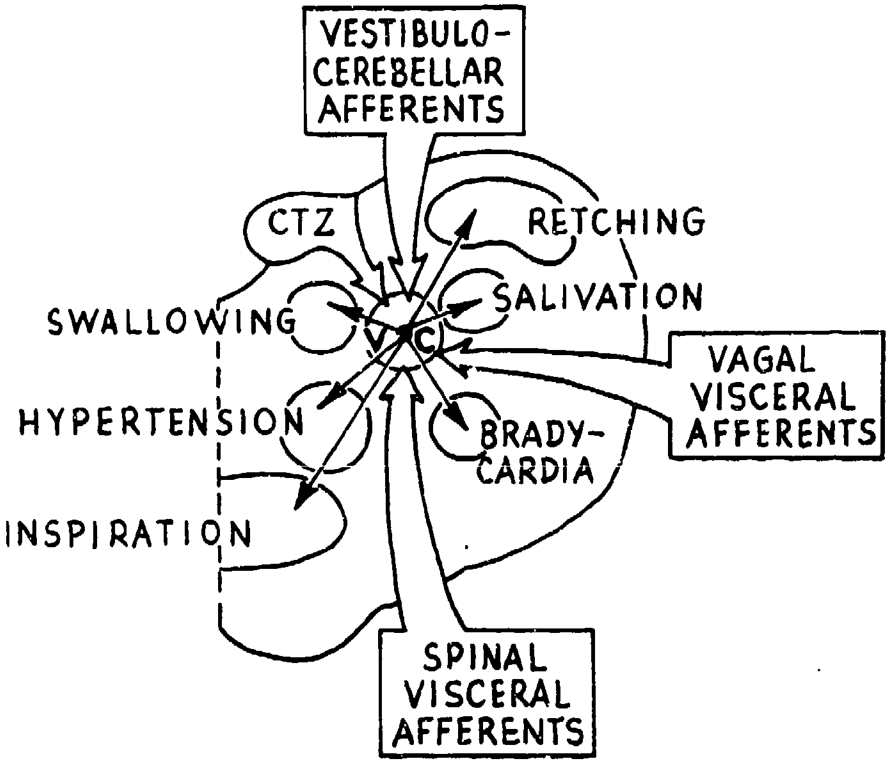

Figure 1. Central organization of the vomiting control mechanism. Diagrammatic cross-section of cat hemi-medulla oblongata rostral to the opening of the spinal canal. CTZ is the chemoreceptor trigger zone for vomiting located in the area postrema on the ventricular margin. VC is the vomiting center in the reticular formation. Four major sources of emetic input, namely, vestibulocerebellar afferents, vagal visceral afferents, spinal visceral afferents, and the CTZ are shown impinging upon VC. The vomiting center coordinates the emetic response by activating the various somatic and autonomic elements involved in the vomiting act.

Surgical ablation of the AP in dogs, cats and humans renders the subjects refractory to a wide variety of chemical emetic agents, now numbering more than 25 substances of both exogenous and endogenous origin (Borison et al., 1984). Of fundamental importance, vomiting responses evocable through other inputs to the vomiting center are in no way disturbed in the postremectomized subjects. Curiously, monkeys do not behave like the other species mentioned respecting the emetic chemosensory function of the AP. According to Brizzee et al. (1955), the AP of the monkey is virtually non-functional as a chemoreceptor trigger zone. A suggested role of the AP in radiation-induced vomiting in the monkey will be given due consideration in sections of this report that follow.

The assignment of a chemical emetic stimulant action in the AP is based almost exclusively on the loss of emetic responsiveness following surgical ablation of that organ. It is also natural to assume that toxic emetic agents which circulate in the blood stream or are injected into the cerebrospinal fluid act on the AP. However, other sites of emetic chemoreceptivity exist both peripherally and centrally in the nervous system (i.e., nodose ganglion and forebrain) which means that the AP is not the universal chemosensor for emesis in the body. Owing to the central location of the AP in the lower brain stem, the possibility must be entertained until disproved beyond a reasonable doubt that surgical damage intended for the AP might unwittingly have interrupted proximate afferent pathways from other sources to the vomiting center, whether of chemosensory or neurosensory origin. Indeed, elimination by postremectomy of vomiting induced pathophysiologically, as was reported for motion sickness, could falsely imply involvement of an endogenous chemical factor in the emetic mechanism (Borison, 1985).

1.1.3 Motor Expression of Vomiting.

A vomiting episode in its typical form consists of three phases, namely, premonitory nausea, repetitive unproductive retching, followed at once by a single forceful expulsion of vomitus. Each phase may occur independently of the others, in different combinations. The retching and expulsive motions are performed by the skeletal (somatic, voluntary) muscles of respiration that produce characteristic transdiaphragmatic pressure surges. When vomiting occurs precipitously with little or no warning in the absence of nausea, the somatic mechanical process is accompanied by minimal autonomic activity. On the other hand, where the mechanical act of vomiting is preceded by a long bout of nausea, extensive recruitment of autonomic activity is developed leading to pallor, cold sweating, salivation, hypotension, tachycardia, diarrhea, etc. The multiphasic reflex nature of the vomiting process involving a variety of inputs and their central connectivity to somatic and autonomic outputs is shown schematically in figure 2. Remarkably, the entire emetic syndrome is effected below the level of consciousness, including the autonomic manifestations of nausea which are elicitable in the decerebrate animal.

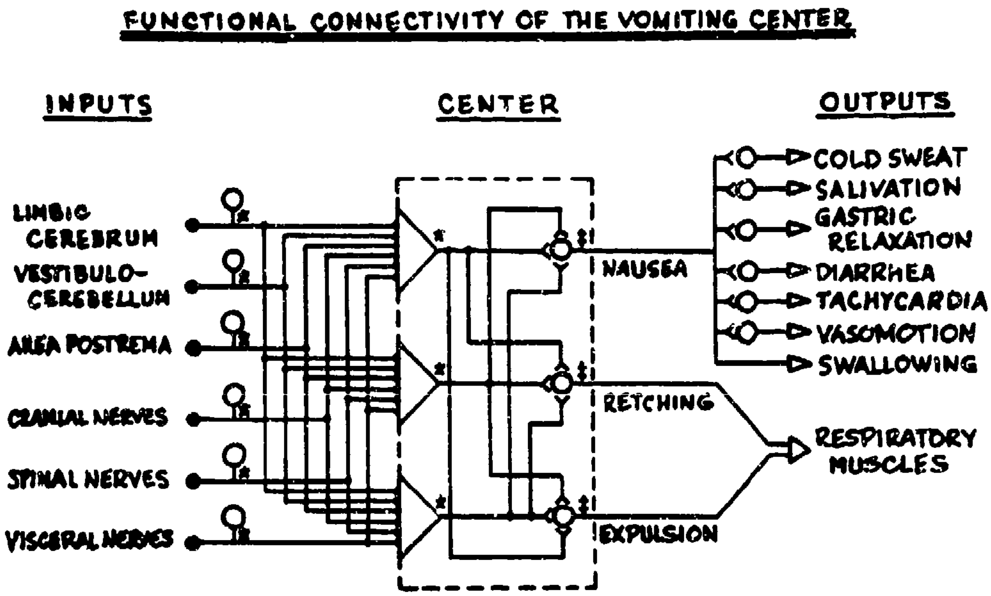

Figure 2. Stylized circuit diagram depicting the functional connectivity of the vomiting center. Each input cell connects centrally via the tractus solitarius with each of three neurons (shown as large triangles) in the nucleus of the tractus solitarius (NTS). These cells of NTS connect preferentially to the processors for nausea, retching and expulsion with reciprocal connections between them. Asterisks at the cell bodies indicate sites of synthesis of neurotransmitters that are transported by axoplasmic flow to the nerve endings. The cell bodies marked with double-crossed lines are motoneurons of final pathways to effectors of vomiting which in all cases synthesize acetylcholine for release by impulses at the axonal endings. The outputs are innervated through autonomic ganglia or by direct efferent connections.

Acute radiation-induced vomiting is generally typified by the full pattern of emetic behavior, but apparent bouts of nausea are not always culminated by retching and the expulsion of vomitus. Thus, emetic activity cannot justifiably be judged as a complete reponse or a real effect without an objective measure of the mechanical act of vomiting. And the act of vomiting is not necessarily completed by the delivery of vomitus when the stomach is empty. The writer has devised a simple non-interfering means of recording the actual intrathoracic pressure excursions in the performance of retching and emetic expulsion with the use of an intrajugular venous catheter which is described below under Research Observations. Surprisingly, the waveform pattern of emesis in the individual animal, i.e., the "emetic signature", is practically unchanged in repeated episodes despite progressive evacuation of the gut.

1.2 STATUS OF INVESTIGATIONS ON ACUTE RADIATION-INDUCED VOMITING.

Present analysis of the emetic process in radiation sickness is restricted to the acute phase that spans the first two days after a capsule exposure to ionizing radiation.

1.2.1 Role of the Area Postrema (AP).

Extrapolating from the emetic control concept presented above, involvement of the AP in radiation-induced vomiting carries with it the implication that a humoral factor operates as an emetic messenger in the afferent limb of the reflex arc. It is agreed from shielding studies that the AP itself, indeed the entire head, is not the sensitive target responsible for the elicitation of emesis after whole body irradiation. Moreover, it is generally accepted that the upper abdomen is the most sensitive radioemetic target. The likelihood of non-humoral involvement of the AP, such that the neural pathway from a peripheral radiosensitive source might pass through the AP or make a synaptic connection in that organ en route to the vomiting center, is without neurophysiological support. A variety of neural terminations and neuroactive agents have been identified in the AP but their functional significance has not been established (Leslie, 1985). It has been speculated that efferent nerves ending in the area postrema may perform ill-defined modulating functions on cardiovascular and or respiratory activities, but reflex initiation through these nerves of an episodic event effected by any of the control systems operating in the lower brain stem has yet to be demonstrated.

Clear lines of conflict exist on radioemetic protection afforded by postremectomy in dogs and cats. In addition to a possible species difference in the culpable radiosensitive target, a difference in the effective dose of radiation and differences in reported time-frames of observation may contribute to the discord between the two groups of studies, discussed in detail in the body of this report. To the point, dogs subjected to postremectomy were found to be protected against acute radiation-induced vomiting whereas cats were not benefited by the operation.

A presumptive radioemetic role of the AP in monkeys deserves separate attention because protection against vomiting in this species was afforded either by postremectomy or by supradiaphragmatic vagotomy, which suggests a common mode of afferent neural interruption producing the end result. This matter is discussed further in its appropriate context below.

Notwithstanding the research status of the AP in radioemesis manifested by dogs and monkeys, our results in cats reported herein excludes the AP as a participating element in the reflex mechanism of radiation-induced vomiting.

1.2.2 Role of Peripheral Afferent Neural Pathways.

The design of a successful therapeutic strategy for radioemetic protection depends crucially on whether the specific vomiting reflex is mediated chemogenically or is "hard-wired" through the vomiting center. We are not immediately concerned here with how the reflex is initiated at its sensory origin, which may or may not involve a local chemical mediator. Rather, our present concern is with the existence of a humoral factor, possibly conveyed through the blood stream, traversing a neural gap in the afferent reflex pathway of radioemesis. As long as the AP is given a credible role in radiation sickness, an afferent humoral factor retains its viability as a reflex link in dogs and monkeys. However, our work in cats leaves no room for participation of the AP or a related chemical factor in the mechanism of radiation-induced vomiting in this species.

Vomiting responses caused by most disorders of the abdominal viscera and especially resulting from gastrointestinal irritation are known to be activated through reflex afferent signals in the vagus and splanchnic nerve trunks (reviewed by Borison and Wang, 1953). On the other hand, it has long been appreciated in clinical practice that pain of visceral origin and the related nausea may not be relieved by section of these nerves. Indeed, Sheehan (1933) demonstrated that free sensory nerve endings in the mesentery do not degenerate on sympathetic and vagus nerve interruption and hence must be supplied by independent afferent spinal nerve elements. Borison (1957) found that radiation-induced vomiting in the cat persisted after section of the abdominal autonomic innervation. By contrast, the vomiting was abolished if, in addition to having been vagotomized, the cat was subjected to dorsal rhizotomy of spinal cord segments T5 through T10. This led to the conclusion that an "extra-sympathetic" afferent nerve pathway, as well as the vagus nerve, is an essential component of the radioemetic reflex input in the cat. Whether the "co-sympathetic" visceral afferent fibers, i.e., those accompanying the sympathetic nerve outflow, are also essential for evoking radioemesis remains to be proved because spinal dorsal rhizotomy indiscriminately interrupts all segmental afferent nerve fibers.

We show in the present report that high dorsal column section of the spinal cord serves in lieu of the segmental rhizotomy, combined with vagotomy, to protect against radioemesis. This surgical maneuver also selectively interrupts one of two populations of afferent fibers from the splanchnic nerves which travel intraspinally as separate distributions in the dorsal and lateral columns, but it is not known whether the dorsal splanchnic centripetal group serves synergistically with the afferent fibers of extra-sympathetic origin responsible for the evocation of radioemesis.

SECTION 2

RESEARCH OBSERVATIONS

2.1 ACUTE RADIATION-INDUCED VOMITING IN AREA POSTREMA-ABLATED CATS.

2.1.1 Introduction.

Numerous emetic agents, endogenous as well as exogenous, have been identified as activators of the chemoreceptor trigger zone in the area postrema (AP), appropriate to its chemosensory function (Borison et al., 1984). On the other hand, the AP has also been implicated in emetic syndromes where mechanisms of chemical activation have not been established, namely as an essential link in the vomiting responses to ionizing radiation and to passive body motion. With respect to the acute stage of radiation sickness, conflicting results have been reported from different laboratories on the protective effect of postremectomy in different species, that is, in dogs (Chinn and Wang, 1954; Wang et al., 1958; Brizzee et al., 1958; Harding et al., 1985; Carpenter et al., 1986), in monkeys (Brizzee et al., 1955; Brizzee, 1956), and in cats (Borison, 1957). Indeed, the investigations in cats and monkeys indicate a subdiaphragmatic neurosensory origin of radiation-induced vomiting. Effects of postremectomy in rats, a species incapable of vomiting, are given separate attention in the Discussion below.

The medulla oblongata, with its AP, is the vital hub of the nervous system to which all visceral sensory nerve inputs are connected. Surgical ablation of targeted structures in this compact part of the brain carries an inordinate risk of producing unwanted and unrecognized damage to neighboring structures. Thus, in considering the two possible extreme effects of postremectomy on radiation-induced vomiting: (1) elimination of the vomiting would require proof of local destruction limited to the area postrema; (2) sparing the vomiting would require proof of complete destruction of the area postrema. As will be shown in the present work, ablation of the AP did not remarkably affect radiation-induced vomiting. Accordingly, our purpose herein is to document lesion morphology for completeness of the AP ablations in cats that vomited unequivocally to ionizing radiation yet were refractory to drug-induced vomiting (Borison et al., 1987b)

2.1.2 Methods.

Experiments were performed on 72 cats, 8 of which were subjected to surgical ablation of the AP. All the cats were full grown, healthy, and unselected for gender. They were kept under observation in our own laboratory quarters for at least a week before being put to experimental use. Every cat had a catheter installed in the superior vena cava and brought out on the back of the neck. This procedure, done in preparation for radioemesis, was performed aseptically with the cat under pentobarbital anesthesia (40 mg/kg, intraperitoneally) at least 4 days in advance of its irradiation to allow sufficient time for full postoperative recovery.

Surgical ablation of the AP was carried out at least one month prior to the day of radiation exposure. The operation was performed aseptically with the use of pentobarbital anesthesia (40 mg/kg, intraperitoneally). The cat was supported on artificial ventilation as a precautionary measure. The AP was ablated by free-hand application of a pencil-type heat cautery. By gross observation, the chronically postremectomized cats were behaviorally indistinguishable from normal. They were, however, neurologically unique in being unresponsive to a normally effective emetic test dose of deslanoside (0.16 mg/kg), a digitalis glycoside, administered intravenously. This test injection was given at least a week in advance of radiation exposure to establish functionally the successful ablation of the AP.

Radiation-induced vomiting was recorded objectively throughout this investigation. Vomiting is a stereotyped form of mechanical activity effected by the respiratory musculature through which the gut is acted upon by highly coordinated pressure surges in the thorax and abdomen (McCarthy and Borison, 1974). The forces generated within the thorax show directional selectivity in the phasic components of vomiting, such that retching (nonproductive surges) is characterized by negative pressure pulses and expulsion occurs as a positive pulse. The vomiting act, differentiable into its retching and expulsion components, was recorded oscillographically by means of a standard strain-gauge transducer attached to the indwelling open-ended catheter placed in the superior vena cava for measuring the intrathoracic pressure. The pressure tracing provided unmistakable identification and timing of emetic behavior over a 24-hour period of continuous recording. A suspensory arrangement for the catheter leading to a rotatable tubular connection passing through the cage ceiling allowed essentially unhampered movement of the cat without disturbance to the recording.

Fifty-eight normal cats and five postremectomized cats were exposed whole-body to ^{60}Co irradiation from an Eldorado cobalt source (AECL Ltd., Ottawa, Canada). Radiation doses varied from 7.5 to 90 Gy. The unanesthetized cat was contained entirely in a vented Plexiglas box allowing some spontaneous body repositioning in the radiation field. The ^{60}Co to target distance was adjusted for a dose rate of 1.0 Gy min^{-1} verified by thermoluminescent dosimeters placed deep in the colon of an anesthetized test subject.

Six normal cats and three postremectomized cats were exposed to unfiltered X-radiation at the dose of 45 Gy measured deep in the colon and delivered at the rate of 0.5 Gy min^{-1} from a Maxitron 300 (GE, Milwaukee WI). During exposure of the body to this form of radiation, the cat's head protruded through an adjustable opening in the holding box and it was shielded from the X-rays. The animal was rotated 180^{o} in relation to the X-ray source halfway through the radiation session.

The behavior of all the cats while they were being irradiated was continuously monitored by closed-circuit television. Radiation exposures were routinely made early in the morning. The cats had regularly consumed the previous evening meal and were offered a small food treat prior to the irradiation.

The cats were maintained for 48 hours after being irradiated and were killed by an overdose of pentobarbital injected intravenously through the indwelling catheter. Brain stem specimens were taken promptly after in situ fixation by transcardiac perfusion of the head with physiological saline followed by 10% Formalin. The tissues were further stored in a solution of l0% Formalin for two weeks before histological processing. The medulla with cerebellum attached was sectioned transversely at 7 to 10 µm through the entire length of the AP. Sections were taken at approximately 0.25 mm intervals to be variously stained with luxol fast blue, cresyl violet, and periodic acid-Schiff methods.

2.1.3 Results.

2.1.3.1 Physiological Form of Radiation-Induced Vomiting. Owing to the episodic nature of the vomiting response to ionizing radiation and to its unpredictability, each occurrence of vomiting was recorded oscillographically as the intrathoracic pressure signal described above.

Figure 3 illustrates variations of recorded emetic behavior both in normal cats and in a postremectomized animal. Individual configurations are evident, but the characteristic pattern of negative pressure deflections indicative of retching followed by the positive spike responsible for expulsion of vomitus is unmistakable in the stripchart recordings. No qualitative difference was detectable between normal and postremectomized cats in their physiological expression of radioemesis.

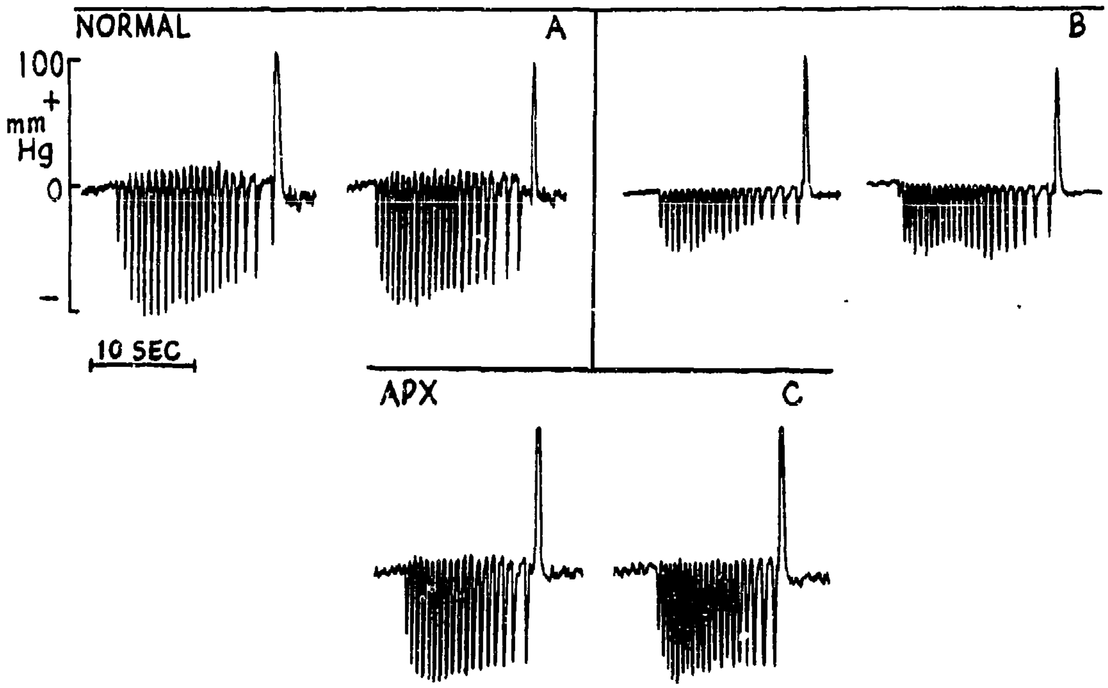

Figure 3. Expanded stripchart recordings of the first and a repeated radioemetic episode obtained as the intrathoracic pressure signal in each of three cats. Panels A and B from NORMAL cats are to be compared with panel C from a postremectomized cat (APX). Note the negative pressure deflections in retching followed by the positive deflection in expulsion.

2.1.3.2 Radioemetic Activity and Postremectomy. The dose-response relationship for the elicitation of vomiting within 24 hours after whole-body exposure to a ^{60}Co source of gamma-radiation, 7.5 to 90 Gy at 1.0 Gy/min, is presented in figure 4.

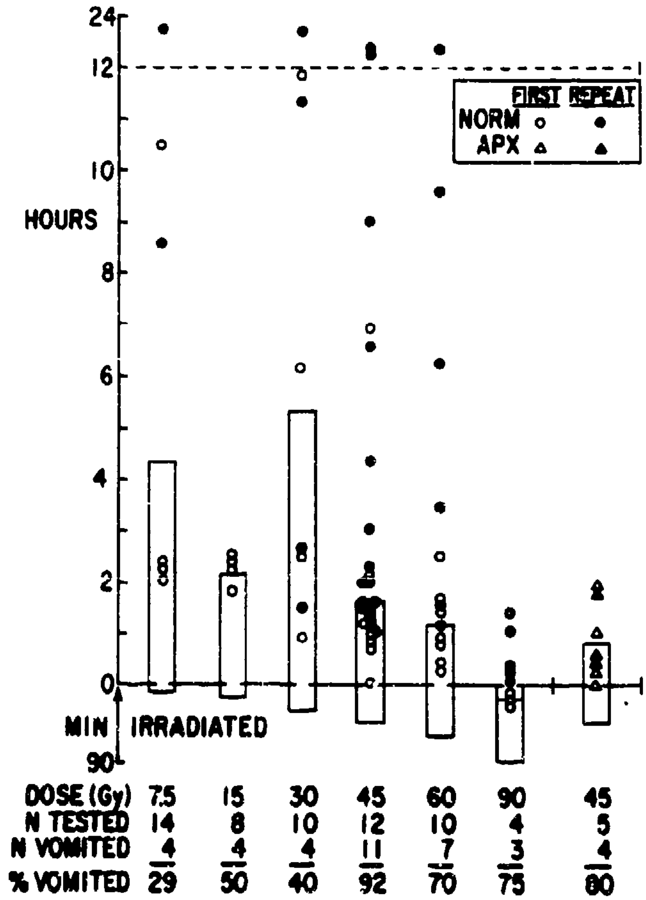

Figure 4. Radioemetic dose-response relationship for ^{60}Co irradiation shown as the initial and repeated episodes of vomiting. Postremectomized (APX) cats, marked by the triangles, were exposed to 45 Gy for comparison with normal cats, marked by the circles, tested over the dose range of 7.5 to 90 Gy. The cross-hatched bars indicate the average postirradiation time to onset of vomiting (for first emetic episodes identified by the open circles). The open bars indicate the time taken for irradiation. Note at 90 Gy that the onset of vomiting occurred before the end of irradiation in all three responsive cats.

The occurrence of first and repeated episodes of vomiting are indicated separately. Vomiting occurred between one and four times in responsive animals, but repeated emesis was evoked consistently only at 90 Gy. No attempt was made with these limited data to judge response severity on the basis of emetic repetition. The average onset time of vomiting, i.e., to the first episode indicated in the figure by the cross-hatched bar height,was reduced from 258 min at 7.5 Gy to 70 min at 60 Gy. An apparent deviation from regular dose-response behavior was found at 30 Gy with a dip in emetic incidence (to 40%) and a bulge in average onset time of vomiting (to 322 min). Emesis occurred before the completion of irradiation at 90 Gy. The highest incidence of vomiting was obtained at 45 Gy, i.e., 92%, with an average onset time of 98 min. This dose of radiation was therefore selected for testing five chronically postremectomized cats, of which four vomited with an average onset time of 48 min, as shown in figure 4. No statistically significant difference was evident by chi-square comparison of emetic incidence or by t-test comparison of onset latency between normal and postremectomized cats. Thus, no protection was afforded by postremectomy against whole-body radiation-induced vomiting from a ^{60}Co source.

In a second series of experiments presented in table 1, a gut dose of 45 Gy X-irradiation (head shielded) evoked vomiting in all of six cats with an average onset time of 27 min. The same radiation treatment evoked vomiting in two of three postremectomized cats with an average onset time of116 min, again demonstrating a non-essential role of the area postrema. Nonetheless, a possible modifying influence of the area postrema on the emetic effect of X-radiation in this small series has not been excluded.

Table 1. Vomiting response to 45 Gy unfiltered X-radiation (0.5 Gy/min at gut with head shielded) in normal and AP-ablated cats.

Condition	Cats Exposed	Cats Vomited	Onset time in min[a] Av. (Range)
Normal	6	6	27 (4-63)
AP-ablated	3	2	116 (46-184)

[a]Latency from end of irradiation to first emetic episode.

2.1.3.3 Histological Verification of Area-postrema Ablation. The AP was ablated in 8 cats, all of which were examined histologically for extent of surgical damage. Figure 5A shows the macroscopic appearance of the normal AP alongside two histological sections, upper and lower, indicated by the horizontal lines through the caudal portion of the fourth ventricle in the medulla oblongata. Arrows point to the AP in each of the panels.

In figure 5B are shown sections taken at approximately the same medullary levels from cats that vomited in response to radiation (+) compared with cats that were refractory (-), separated according to ^{60}Co or X-ray exposure. Specimens from two additional cats that responded to ^{60}Co irradiation were not remarkably different from the examples selected for illustration in the figure.

The following facts are evident from histological evaluation of the operated brain specimens (1) The AP was completely destroyed in every case. (2) Surrounding structures were largely spared. (3) Greatest damage was evident adjacent to the AP and the overlying cerebellum in the case of the animal that failed to vomit in response to X-irradiation. Therefore, destruction of the AP per se cannot be held accountable for the presently observed instances of emetic inactivity following an exposure to ionizing radiation.

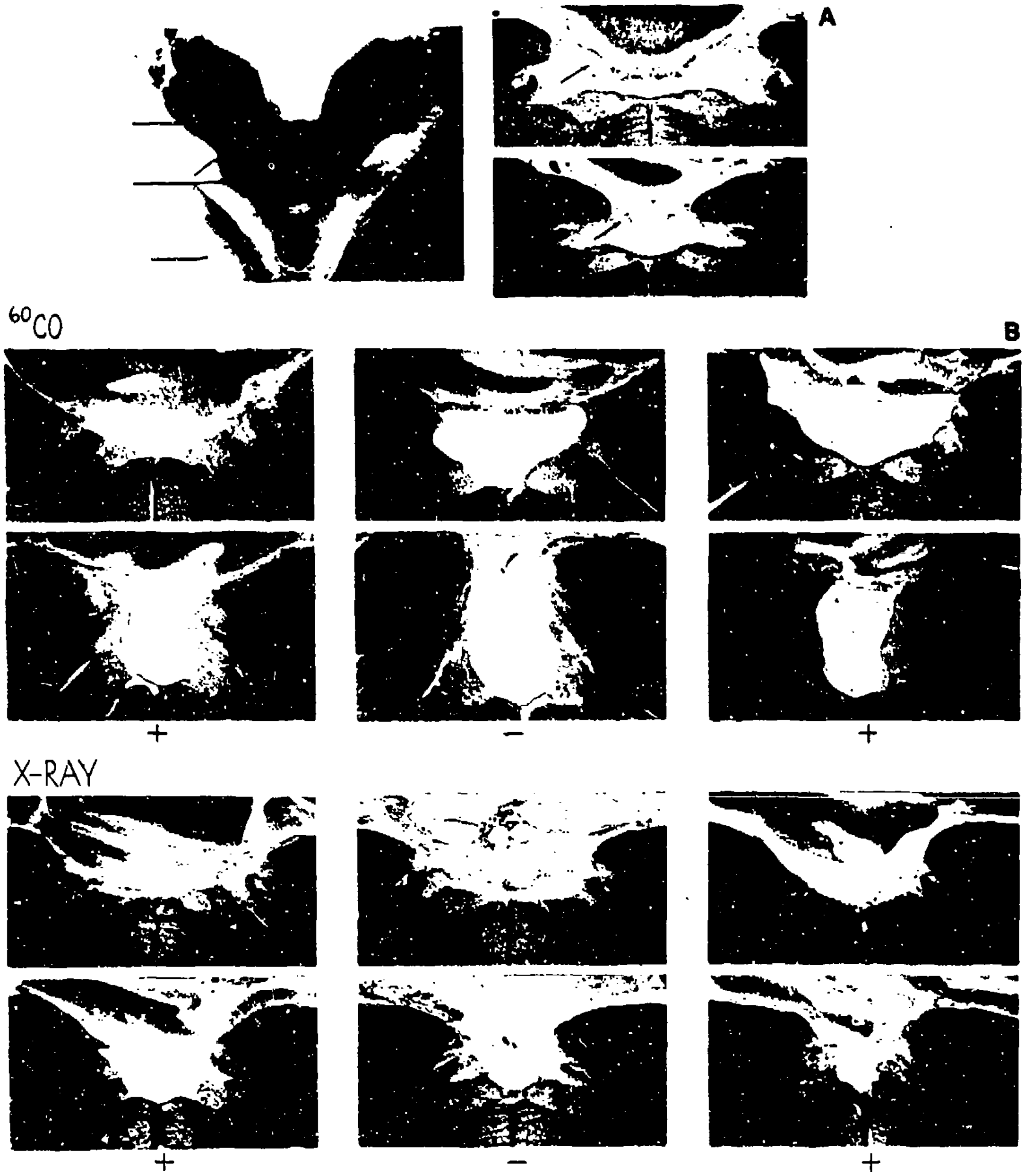

Figure 5. Lesions of the AP in irradiated cats.

Part A: Left - normal AP in the caudal medulla oblongata seen macroscopically at arrow; calibration bar is 1.0 mm. Right - tissue sections taken through medullary levels indicated on left, with arrows pointing to the AP.

Part B: Medullary sections from postremectomized cats at about the same levels as shown in the normal specimen. Upper set taken from three cats exposed to ^{60}Co radiation. Lower set taken from three cats exposed to X-radiation. In each set, the cat in the center (-) did not vomit after its irradiation by contrast with those on both sides (+) that yielded radioemetic responses.

2.1.4 Discussion.

2.1.4.1 Nature of Radiation-Induced Vomiting. To our best knowledge, radioemesis has not previously been characterized physiologically as an expression of the actual body intracavity pressure changes responsible for oral evacuation of the gut. As with drug-induced vomiting, the emetic effect of radiation in a single episode recorded from the thoracic cavity consists typically of two phases. Initial repetitive negative pressure pulses during non-expulsive retching in the first phase are followed at once by a positive pressure surge in the second phase that ejects the contents of the upper gut (McCarthy and Borison, 1974). It should be emphasized that the physiologic pattern of successive episodes remains essentially unaltered despite the loss of gut content. No difference was evident in the character of radiation-induced vomiting recorded from postremectomized cats by comparison with responses obtained in normal cats. Since the AP serves only as a trigger of vomiting, it is not surprising that an emetic response which is initiated through another input to the vomiting center retains its typical character in the postremectomized animal.

2.1.4.2 Discordant Reports on the Role of the AP. Six papers appeared from 1954 to 1958 concerning the effects of postremectomy on radioemesis in dogs, monkeys and cats (Chinn and Wang, 1954; Brizzee et al., 1955; Brizzee, 1956; Borison, 1957; Brizzee et al., 1958; Wang et al., 1958). The time frame for scoring acute emesis varied from 2 to 6 hours of direct observation in dogs and monkeys, and up to 10 hours in cats. In no case was vomiting recorded objectively. Drug confirmation of emetic refractoriness resulting from successful trigger-zone ablation was carried out in three of the studies (Chinn and Wang, 1954; Borison, 1957; Wang et al., 1958). In the separate studies with dogs (Wang et al., 1958; Brizzee et al., 1958), Contrary claims were made on whether "total" destruction of the AP (or trigger zone) was needed to obtain a protective effect against radioemesis. The case for adequacy of subtotal destruction was made on the basis that a number of the lesioned animals which were unresponsive to radiation still vomited to the injection of apomorphine (Wang et al.,1958). contrariwise, the claim for the indispensability of total destruction was based on histological grounds where incomplete ablation of the AP was found in those operated that were not protected against radioemesis (Brizzee et el., 1958).

Monkeys are resistant to emetic drugs that commonly act on the AP in dogs and cats, thus invalidating this kind of pharmacological test for successful postremectomy in simian species (Brizzee et al., 1955). Furthermore, monkeys may retain vomitus in their cheek pouches for later reingestion, thereby confounding the visual detection of emesis in these animals.

Histological documentation of surgical lesions was provided in four of the aforementioned publications (Brizzee et al., 1954; Brizzee et al., 1955; Brizzee, 1956; Borison, 1957). Some damage to contiguous structures was reported in every study in which this organ was identified as the essential element in radioemesis. Indeed, even lesions intended for surounding structures occasionally resulted in radioemetic refractoriness, but this outcome was attributed to associated damage of the AP.

Most remarkably, Brizzee (1956) demonstrated that supradiaphragmatic vagotomy provided full radioemetic protection in the monkey, which suggested that adventitious central damage to vagal sensory nuclei could account for the effect of "postremectomy". Borison (1957) reported that viscerosomatic afferent nerve input from the upper abdomen was the sufficient sensory source for radioemesis in cats, while disallowing an essential role for the area postrema. Wang et al. (1958) contradicted this contention but described nonetheless a definite prolongation in onset of radiation-induced vomiting and even some loss of emetic responsiveness in dogs and cats that had been subjected to apparently incomplete denervations of the abdomen.

Recently, new attempts were made to resolve the problem of AP involvement which again implicated this structure as essential for radioemesis in dogs (Harding et al., 1985; Carpenter et al., 1986). Unfortunately, the lesions described in those works extended to surrounding structures of the AP.

It is common knowledge that rats do not vomit, yet these animals display responses to ionizing irradiation that coincide with extra-emetic elements of radiation sickness observe in species capable of vomiting. The effects of postremectomy were investigated in different laboratories on conditioned taste aversion (Rabin et al., 1983; Ossenkopp, 1983) and delayed gastric emptying (Harding and Ossenkopp, 1983) produced by ionizing radiation in rats. Consistent attenuation of taste-aversion behavior was reported in full publications, and protection against gastric stasis was reported only in summary form. Interpretation of these findings is complicated by two considerations: (1) No chemical test of the kind that establishes emetic refractoriness in vomiting species is available for functionally validating the success of postremectomy in the rat. (2) Although abdominal irradiation is a sufficient stimulus for producing the described behavioral effects in rats, abdominal denervations and vagotomy in particular were not carried out in the aforementioned studies as a control procedure for possible adventitious central interruption of visceral afferent pathways accompanying the postremectomies.

In evaluating those reported findings in postremectomized rats alongside the present observation that radioemesis persists after postremectomy in cats, it is conceivable that extra-emetic signs of sickness might still be mediated by the AP. But we could not distinguish between properly lesioned and normal cats in their manifestations of the entire radioemetic syndrome.

2.1.4.3 Connection to Motion Sickness. With widening opportunities for human exposure to ionizing radiation, there is a growing likelihood that radiation will be encountered by persons in moving vehicles, particularly in military circumstances. In a laboratory study on rhesus monkeys, Mattsson and Yochmowitz (1980) showed that when body motion was applied simultaneously with exposure to ^{60}Co radiation, it reduced the ED_{50} for radioemesis from 4.46 to 2.58 Gy, which they regarded as evidence of interaction of two nauseating stimuli. Of related clinical interest, Morrow (1984) revealed in cancer patients a correlation between emetic responsiveness to radiomimetic chemotherapy and susceptibility to motion sickness.

In the present study, we used cats that were examined also for motion-induced vomiting (Borison and Borison, 1986). There is a noteworthy parallelism in the literature on involvement of the AP in radiation sickness and in motion sickness (Borison, 1985). contrary to the general perception, our work supports the position that the AP is not an essential element in either of the syndromes. This disgreement can best be explained by entertaining the possibility that, in other laboratories, inadvertant interruption of nearby critical sensory nerve inputs to the emetic center could have occurred unwittingly during surgical ablation of the AP.

A presumptive association of the motion and emetic syndromes with the AP taken together with indications of their pathophysiologic interaction naturally suggests that a common mode of therapy might be found that blocks transmission of both activities through the AP. Such investigations have not to our knowledge been rewarding and are not further encouraged by our own laboratory observations.

2.1.4.4 The Radioemetic Target. A large body of evidence in the literature points to the upper abdomen as the most sensitive site of exposure for eliciting radioemesis. Denervation studies have demonstrated furthermore that the abdominal radiosensitive target is "hard-wired" for emetic signal detection. This means that any chemical factor operating centrally would have to be generated somewhere downstream in the input pathway of the vomiting reflex arc. No such chemical source has been recognized, nor is a chemoreceptive mechanism available for emetic activation according to the present work. It appears therefore, that the most urgent problem for understanding radioemesis is identification of its specific sensory origin in the abdomen.

2.1.5 Conclusions.

The experimental observation reported herein that radiation-induced vomiting in cats is not prevented by structurally complete and functionally verified ablation of the AP leads to two basic conclusions. (1) A complete emetic pathway for radioemesis bypasses the AP. (2) Radioemesis does not depend upon the generation of a chemical factor that selectively activates the AP.

2.2 RADIOEMETIC PROTECTION AT 24 HOURS AFTER ^{60}Co IRRADIATION IN BOTH NORMAL AND POSTREMECTOMIZED CATS.

2.2.1 Introduction.

We showed in studies on cats that chronic ablation of the AP afforded no protection against radiation-induced emesis (Borison,1957; Borison et al., 1987b). By contrast, we found that combined interruption of afferent pathways in the vagus nerve and spinal cord prevented the radioemetic response (Borison, 1957; Borison et ai.,1987a; Section III below). We observed in the course of our work on radiation sickness in normal as well as postrema-ablated cats that great clinical improvement was manifested on the day following irradiation at lethal dose levels, as has been described in man and other species (Miller et al., 1958; Wilson, 1959; Mattsson et al., 1984). The question arises whether the apparent recovery, although temporary, occurs passively through exhaustion of the acute radiation effect or results from the mobilization of a counteractive process. We tested this question by submitting cats to a second dose of radiation on their day of radioemetic remission. The results to be described show that cats in the recovery phase after lethal irradiation are selectively protected in a dose-related manner against acute reactivation of radiation sickness, and that this protective effect of prior irradiation does not depend on the integrity of the AP.

2.2.2 Methods.

This study was performed on 57 cats 5 of which were subjected to chronic surgical ablation of the AP located in the medulla oblongata, i.e., postremectomy. All of the cats were full grown, healthy and unselected for gender. They were kept under observation in our own laboratory quarters for at least a week before being put to experimental use. Every cat had a catheter installed in the superior vena cava and brought out on the back of the neck. This procedure, done in preparation for recording radioemesis, was performed aseptically with the cat given pentobarbital for anesthesia (40 mg/kg intraperitoneally) at least four days in advance of the irradiation.

A number of the animals under present consideration were included previously in our radioemetic dose-response data reported for a single radiation exposure (Borison et al.,1987b), and the lesions of the same postremectomized cats tested herein with double exposure were validated histologically in that study. Surgical ablation of the AP was carried out aseptically with the use of pentobarbital anesthesia (40 mg/kg intraperitoneally) at least a month prior to the time of irradiation. The chronic lesioned cats were behaviorally indistinguishable from normal, but they had become unresponsive to the regular emetic test dose of a digitalis glycoside (deslanoside, 0.16 mg/kg intravenously).

Radiation-induced vomiting was recorded objectively throughout this investigation as intrathoracic pressure deflections on an ink-writing polygraph signalled through the abovementioned intracaval venous catheter. Emetic activity was observed for 48 hours from the initial exposure to radiation. Details of the radioemetic recording characteristics are given above (Borison et al.,1987a).

Each of 46 cats was given two whole-body radiation exposures, separated by an interval of 24 hours, from a ^{60}Co source (AECL Ltd, Ottawa, Canada). Radiation doses varied from 7.5 to 60 Gy. The unanesthetized cat was contained entirely in a vented Plexiglas box allowing some spontaneous repositioning in the radiation field. The ^{60}Co to target distance was adjusted for a dose rate of 1.0 Gy/min verified by thermoluminescent dosimeters placed deep in the colon of an anesthetized test subject. Eleven more normal cats received only a single dose under identical conditions of irradiation and, on the next day, instead of a second radiation exposure they were given an injection of xylazine (0.66 mg/kg intravenously) to compare the effect on vomiting evoked by an unrelated chemical emetic stimulus.

The behavior of all the cats while they were being irradiated was continuously monitored by closed circuit television. Radiation exposures were routinely made early in the morning. Daily mealtime is set at 3 PM in our laboratory and the cats are given in addition a breakfast treat which was provided as usual before each irradiation.

2.2.3 Results.

2.2.3.1 Comparison of Radioemetic Sensitivity on First and Second Irradiation. Emetic responses were recorded in six groups of 5 to 10 cats exposed to whole-body ^{60}Co irradiation on two successive days with doses ranging from 7.5 to 60 Gy (table 2). The same dose was given on both occasions except in one group that received 30 Gy on the second day after a prior dose of 7.5 Gy. The group of 7 cats exposed to 45 Gy includes 5 postremectomized animals. These are given detailed consideration in the next section. The lesioned cats were indistinguishable from normal with respect to radioemetic behavior and are therefore combined with the general population in the dose-effect analysis. Table 2 comprises the emetic responders in all groups observed for 24 hours and reports their average latency to emesis.

Table 2. Radioemetic response frequencies and latencies in cats after each of two exposures to whole-body doses of ^{60}Co radiation (7.5 to 60 Gy separated by an interval of 24 hours.

Dose[a] Gy	N	First Exposure Emesis No. (%)	First Exposure Av. Latency[b] (min)	Second Exposure Emesis No. (%)	Second Exposure Av. Latency (min)
7.5	8	2 (25)	384	5 (63)	598
7.5	6	2 (33)	128	1 (17)	136[c]
15	10	4 (40)	121[d]	5 (50)	942[d]
30	10	4 (40)	322	1 (10)	1380
45	7[e]	5 (71)	117	0 (0)	--
60	5	4 (80)	78	0 (0)	--

[a]Dose rate at 1 Gy/min for all doses.
[b]Time from end of irradiation to first emetic episode.
[c]Data in box is for second exposure at 30 Gy.
[d]Latency is significantly longer after second exposure ($p<.05$ by t-test).
[e]Five of these cats were postremectomized.

The results are further depicted graphically in figure 6 to show the log dose-emetic response relationship. In the figure, emetic responses recorded only within 12 hours after the second irradiation are plotted separately as a subset for comparison with responses of the same cats to the first irradiation which in every case began within 12 hours.

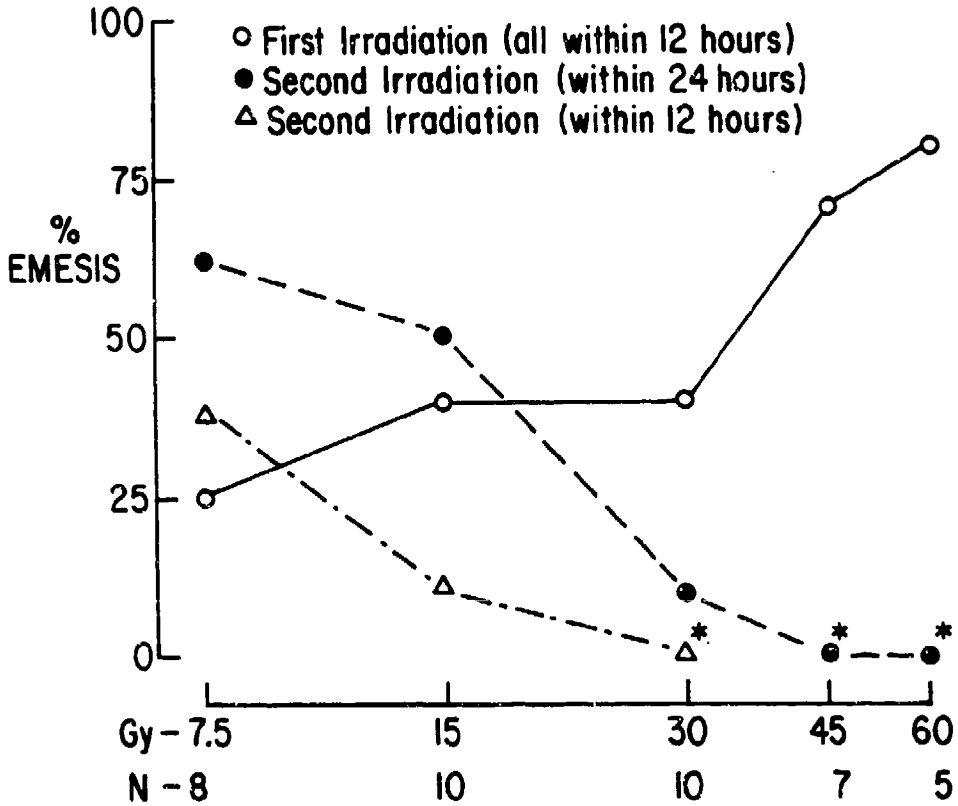

Figure 6. Percentage of acute emetic responders on first and second exposures to ^{60}Co radiation in groups of cats irradiated with doses of 7.5 to 60 Gy scaled logarithmically. All responding cats after the first exposure vomited with a latency less than 12 hours. Some of the responding cats after the second exposure to 7.5, 15 and 30 Gy vomited with a latency greater than 12 hours; these are included in the cumulative points for 24 hours (shown as filled circles). The zero percentages of responders after the second exposure at 30, 45 and 60 Gy, identified by the asterisks, are significantly different from the same group responses after the first exposure.

It is evident from the data that the first irradiation yielded a direct monotonic dose-response relationship with emetic responsiveness increasing from 25 to 80% over the range of 7.5 to 60 Gy (figure 6), and the average emetic latency decreased stepwise for the most part from 384 to 78 min but for the unexplained prolongation at 30 Gy (table 2). By sharp contrast, the emetic results of the second irradiation showed a reversal of pattern from that of the first irradiation, with an apparent crossover of radioemetic sensitivity for the two exposures occurring at the dose of 15 Gy. For the full 24-hour period of observation after the second dose, complete protection against emesis resulted from prior irradiation at 45 and 60 Gy; and for the period of 12 hours, complete protection was afforded additionally at 30 Gy of prior irradiation. The points of zero emetic incidence marked in figure 6 with an asterisk are significantly different by chi-square analysis ($p<.05$) from the same group responses produced with the first irradiation. Although the data for 7.5 Gy are not sufficient for obtaining statistically significant differences, the gross trend indicates if anything that dose repetition at the low end of the range facilitates rather than suppresses radioemetic sensitivity. On the other hand, an emetic blocking effect of 7.5 Gy given initially was revealed when the second dose of radiation was raised to 30 Gy.

2.2.3.2 Radioemetic Protective Effect of Prior Irradiation Persists in Postremectomized Cats. The lesioned cats employed herein for double radiation exposure at 45 Gy (table 2) were described above with morphological documentation as part of our study on radioemesis in cats after a single exposure. Separate examination of the five postremectomized cats in the present series of experiments reveals that none responded after re-irradiation although four of them had vomited after the first exposure. This blocking effect of prior irradiation on radioemesis in the lesioned cats is statistically significant at $p=.01$ by chi-square analysis. Thus, chronic ablation of the AP neither confers protection against radiation sickness that normally results from a single exposure nor does it interfere with the subsequent radioemetic protection as is afforded in normal cats to a second exposure after 24 hours.

2.2.3.3 Specificity of Radioemetic Protection by Prior Irradiation. To test the question of specificity in the development of emetic refractoriness to radiation, we tested a separate set of normal cats with the emetic drug xylazine (0.7 mg/kg, iv) at 24 hours after an initial exposure to 45 Gy ^{60}Co radiation. Without exception, all of 11 cats that experienced vomiting on the day of irradiation also vomited in response to the injection of xylazine given on the next day. The emetic response to xylazine was elicited at the time when full radioemetic protection was shown to be developed in our cats that received double radiation exposure (table 2). The lack of protection afforded by prior irradiation against xylazine-induced emesis (11 of 11 vomited) is significantly different from the blockade of radioemesis (0 of 7 vomited) with $p<.001$ by chi-square analysis. Furthermore, the emetic action of xylazine is known to be mediated through the area postrema (Colby et al.,1981). Thus, it is demonstrated that the area postrema: (a) is not essential for the evocation of radioemesis on first exposure; (b) is not essential for the protective effect of prior irradiation; (c) continues to function chemoreceptively to initiate drug-induced emesis during the state of radioemetic refractoriness. We conclude therefrom that the blockade of radiation sickness by prior irradiation results from specific development of radioresistance.

2.2.4 Discussion.

2.2.4.1 Mechanism of Radiation-Induced Vomiting. Current understanding of the vomiting control system rests on concepts originated by Borison and Wang (1953). Crucial to the resolution of mechanism in acute radioemesis is ruling in or out the involvement of a chemogenic factor. All our work in cats (Borison,1957; Borison et al.,1987a; Borison et al.,1987b) proves that a circulating chemical factor is not involved and that the primary emetic chemoreceptor organ, i.e., the AP of the medulla oblongata, does not participate in the process of radiation-induced vomiting. We have demonstrated instead that acute radiation sickness is neurally mediated by afferent pathways from the upper abdomen traversing the vagus nerves and dorsal columns of the spinal cord (Borison,1957; Borison et al.,1987a). This is consistent with experience in clinical radiotherapy (Danjoux et al., 1979; Court Brown, 1953) and shielding experiments in animals (Borison,1957). Establishing the precise sensory origin of radioemesis is the first essential step for identifying vulnerable sites of therapeutic blockade in radiation sickness.

2.2.4.2 Question of Species Difference. Distinct differences are evident among "vomiting species" in the dose requirement for the evocation of radioemesis in particular (Borison et al., 1987b; Mattsson and Yochmowitz, 1980; Mattsson et al., 1984) and in their responsiveness to emetic agents in general (Borison and Wang 1953; Brizzee et al., 1955), even though the range of radiation lethality in the same species is comparatively narrow (Rugh,1953). Cats are least sensitive to radiation-induced vomiting, whereas monkeys are least sensitive to other forms of emetic provocation while dogs, if not humans, are the most sensitive. The basic question arises whether the observed differences in radioemetic susceptibility among species results from biological variation in excitation threshold of an archtypal sensory receptor, or is an expression of inherently different pathophysiological mechanisms. For the most part, support for different mechanisms in different species rests on observations of radioemetic protection reported in dogs with lesions of the AP suggesting that a humoral factor may be involved at least for low-dose irradiation. As we have discussed above in detail, we believe that inadvertant peripostremal damage could reasonably account for the apparent beneficial effect other investigators have attributed to postremectomy per se in dogs.

2.2.4.3 Nature of the Radioemetic Resistance to a Second Irradiation. Two well described radiobiologic phenomena bear upon the present observation of radioemetic protection: (1) the interposed clinical recovery phase after a lethal exposure; (2) the mollifying influence of two-dose fractionation on the severity of the response to large total radiation doses.

It was early appreciated from hopeless casualties of the atom bomb in Japan that a deceptive state of recovery followed the prodromal emetic phase on the second and third days after the explosions which then deteriorated within a week into a severe terminal enterocolitis (Gerstner,1958). This pattern has been observed in a variety of species. Chaput and Kovacic (1974) reported the effects in miniature pigs of dose fractionation up to an interval of 51 hours between two whole-body doses of 44 Gy mixed gamma-neutron radiation. Those authors showed that the provoked clinical signs were less severe and the performance of a learned task was less disturbed after the second irradiation than the first. In agreement with our present observation they found that initial exposure to smaller though still supralethal radiation doses, e.g., 15 Gy, tended to aggravate the effects of a second exposure. The phenomenon of radiation protection by prior exposure was further examined in miniature pigs exposed to head irradiation only (Chaput and Berardo,1974). Remarkable radioresistance of the brain developed within 30 min after an initial exposure to 44 Gy LINAC radiation. The investigators concluded that physicochemical processes could not adequately account for the observed radioprotective effect against a second dose. The matter of vomiting was not addressed in these studies of dose fractionation in miniature pigs. In another work on fractionated x-irradiation in two equal doses to mice, rats and hamsters, Andrews (1960) concluded that an active recovery component with a half-time of about 8 hours resulted after even massive whole-body radiation doses up to 600 Gy. From a comparison of doses leading to "CNS death" in mice, Yuhas (1969) stated that higher dose rates and larger conditioning doses are better able to induce a protective mechanism which reduces the effectiveness of subsequent exposures.

2.2.5 Conclusions.

The present observations on radiation sickness in cats are consistent with earlier reports on the acute development of radioresistance after supralethal irradiation in other species. We have demonstrated furthermore that the effect is not simply stress related but is selective for ionizing radiation since vomiting is still elicitable by administration of an unrelated chemical stimulus during the phase of radioemetic protection. This finding means also that those neural elements of the reflex pathway performing input detection, central emetic integration and output expression continue to function normally. It follows by the process of elimination that the radioemetic sensory target in the upper abdomen, as the last remaining reflex element, must become desensitized after high dose irradiation as a logical explanation for the self-protective phenomenon observed in double radiation exposure.

2.3 HIGH DORSAL COLUMN CORDOTOMY PLUS SUBDIAPHRAGMATIC VAGOTOMY PREVENTS ACUTE RADIATION SICKNESS IN CATS.

2.3.1 Introduction.

Borison (1957) identified an extrasympathetic spinal afferent pathway, evidently originating from an abdominal visceral source, as a neural mediator of radiation-induced vomiting in cats. In the same study, it was shown that the emetic chemoreceptor trigger zone in the AP was not essential for effecting the emetic response. The non-essential nature of the AP has been reaffirmed by us in a more thorough investigation on cats (Borison et al., 1987b), and reported herein. Nevertheless, an essential role of the area postrema is still contended for the vomiting caused by radiation in dogs as discussed above in detail.

The present study in cats was undertaken to test the hypothesis originally advanced by Borison (1957) that the responsible spinal afferent pathway in radiation sickness approaches the emetic center through the dorsal column nuclei where it is vulnerable to damage in experimental surgery on the caudal medulla. Accordingly, our research strategy was to sever the putative dorsal column fibers as high as possible while avoiding damage to the AP. The results to be described demonstrate that this operation on the upper spinal cord combined with subdiaphragmatic vagus nerve section prevented radiation-induced vomiting without involvement of the AP. Indeed, the surgical deafferentations ameliorated the entire acute sickness syndrome (Borison et al., 1987a). The peripheral radioemetic sensory target yet remains to be found.

2.3.2 Methods.

Experiments were performed on 24 fully grown cats of either sex, 12 of which were subjected under sterile conditions to chronic surgical procedures of high spinal cordotomy, subdiaphragmatic vagus nerve section or both. Every animal was in excellent health when selected for the experiment, none died as a result of the neurological surgery, and all the operated cats recovered their well-being prior to being irradiated. About two weeks was allowed for convalescence between the last neurosurgical procedure and the radiation exposure.

2.3.2.1 <u>High Dorsal Cordotomy.</u> The cats were anesthetized with pentobarbital Na (40 mg/kg i.p.), intubated to provide a free airway, and maintained on artificial ventilation as a precautionary measure. The upper-cord lesion site was approached as for ablating the AP, that is, by retraction of the nuchal muscles from the midline over the occipital bone extending downward to the 2nd vertebra thereby allowing clear access to the atlanto-occipital membrane. However, a craniotomy was not needed to reach the subdural surface at the bulbospinal junction; only the ligamentous membrane was incised transversely for clear visibility of the dorsal columns and cerebellar nodulus overlying the obex. The dorsal funiculus and nuclei were severed about 1 mm caudal to the obex (fig. 7).

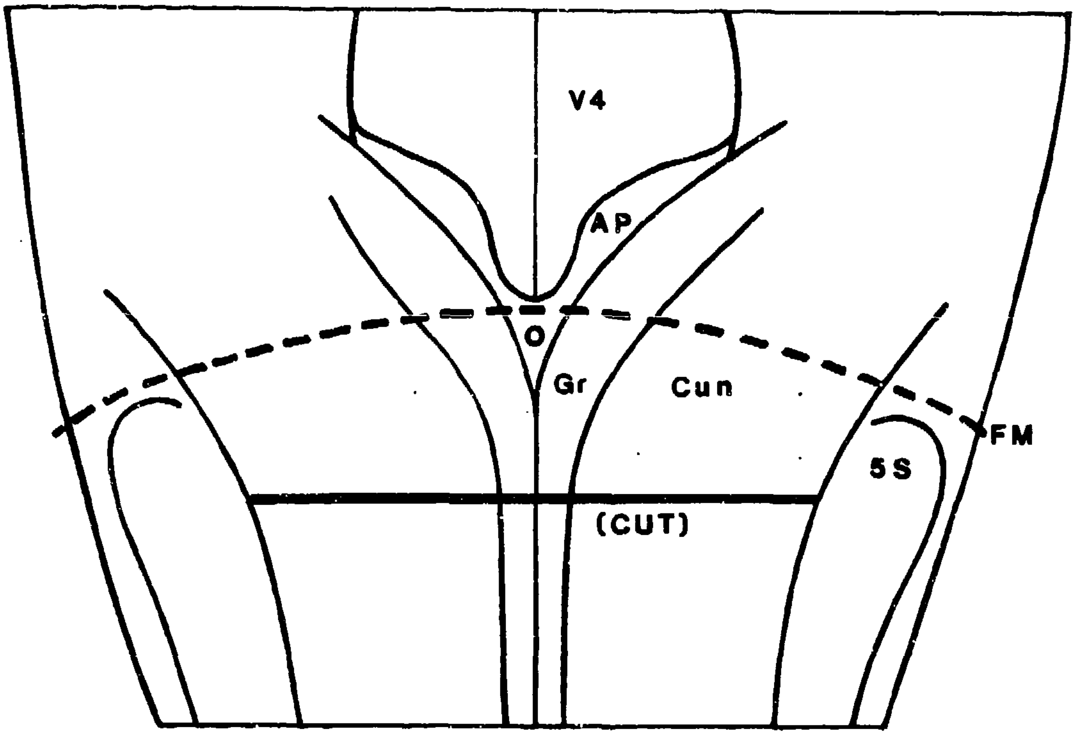

Figure 7. Regional topography of the bulbospinal operative site showing the relationship of the dorsal cordotomy (CUT) to the area postrema (AP). The cerebellar nodulus was omitted for the sake of clarity but is normally visible at the foramen magnum (FM) where it may completely cover the obex (O). Other labelled structures are: V4-fourth ventricle, Gr-gracile nucleus, Cun-cuneate nucleus, 5S-spinal nucleus of the fifth cranial nerve.

The dorsal cordotomy was accomplished by making shallow pial stabs bilaterally with fine pointed scissors, avoiding blood vessels, and spreading the points sufficiently to allow manual insertion of a sharp bent spatula (2 mm wide) which was then pushed down 2 mm on each side and finally moved medially to complete the incision started contralaterally. Bleeding was minimal and no attempt was made to repair the dura mater. A small pad of Gelfoam was placed on the dural opening in the first few cats but this was omitted without consequence in the remainder. The nuchal muscles were sutured in layers and the skin was closed with a subcutaneous hidden stitch that required no further attention. Combiotic (penicillin and streptomycin) was injected intramuscularly. Emergence from anesthesia was unremarkable. Details on postoperative behavior are given in the Results.

2.3.2.2 Subdiaphragmatic Vagus Nerve Section. The cats were anesthetized as described above. Artificial ventilation was employed in this procedure to prevent a possible pneumothorax produced inadvertantly by diaphragmatic puncture during circumesophageal manipulations. A midline abdominal incision was made extending caudally about 10 cm from the xiphisternum. The gastroesophageal junction was mobilized and firmly retracted from the diaphragm. The vagus nerve branches were not individually dissected, as small bundles may thus escape detection. Instead, three longitudinal incisions were made about equidistantly through the adventitial layer down to the muscularis in the region of the cardiac sphincter. Three pairs of silk ligatures (size 00) were then tunneled under the adventitia, with the vagus nerves contained therein, to completely encircle the lower esophagus. The apposed ligatures were then pulled apart and tightly tied in place as a group prior to cutting between them for complete separation of rostral and caudal rings with muscularis exposed all the way around. A suspect free nerve branch was cut for good measure in two cases. The abdominal wall was closed with interrupted mattress sutures, and the skin was closed with a running subcutaneous hidden stitch that required no further attention. Combiotic was administered as usual. These cats were maintained postoperatively on meals in divided portions to avoid the spontaneous occurrence of postcibal emesis.

2.3.2.3 Recording of Radioemesis. Radiation-induced emesis was recorded oscillographically as its characteristic intrathoracic pressure pattern signalled through a standard strain-gauge transducer connected to a saline filled catheter in the superior vena cava. For this purpose, every cat was anesthetized at 3 or 4 days before its time of irradiation and had a catheter introduced aseptically into an external jugular vein and advanced into the thorax. The free end of the catheter was brought out as a short pigtail at the back of the neck. A suspensory arrangement for connecting the catheter to the transducer allowed essentially unhampered movement of the cat. The vomiting act was differentiable by this means into its mechanical components of retching, represented by a series of negative pressure deflections, and of expulsion expressed as a single positive spike. The pressure tracing provided unmistakable identification and timing of emetic behavior over a 24-hour period of continuous recording. In the event that a cat did not vomit in response to the radiation stimulus, it was tested with an emetic dose of a digitalis glycoside, deslanoside (0.16 mg/kg i.v.), which invariably evoked vomiting.

2.3.2.4 Radiation Exposure. All the cats were exposed whole-body to ^{60}Co irradiation from an Eldorado cobalt source (AECL Ltd., Ottawa, Canada) at the constant radiation dose of 45 Gy. The unanesthetized cat was contained entirely in a vented Plexiglas box allowing some spontaneous body repositioning in the radiation field. The ^{60}Co source-to-target distance was adjusted for a dose rate of 1.0 Gy/min verified by thermoluminescent dosimeters placed deep in the colon of an anesthetized subject. The behavior of every cat was monitored by closed circuit television during the irradiation. Radiation exposures were routinely made early in the morning. The cats had regularly consumed their previous evening meal and were given a small breakfast treat prior to the irradiation.

2.3.2.5 Postmortem Management and Lesion Histology. The cats were generally allowed to survive for 48 hours after having been irradiated and some were exposed to a second dose of radiation at 24 hours as part of another study. They were killed by an overdose of pentobarbital or deeply anesthetized for brain perfusion. Brainstem specimens, when required, were taken promptly after in situ fixation by transcardiac perfusion of the head with physiological saline followed by 10% Formalin. The tissues were further stored in a solution of 10% Formalin for at least two weeks before histological processing. Specimens from all the upper-cord operated cats were embedded in paraffin after detaching the cerebellum and were cut either horizontally or transversely at a thickness of 20 µm. Tissue sections were taken through the entire lesion at approximately 0.2 mm intervals for staining with luxol fast blue plus cresyl violet.

All vagotomized cats received a careful post-mortem exploration of the thorax and abdomen to trace the vagus nerves and validate their complete interruption. In one case, where the vagotomy was combined with dorsal cordotomy, a vagal branch was found to be unsevered. This cat, which had vomited after irradiation, was excluded from the data analysis.

2.3.2.6 Data Analysis. The chi-square test was employed for statistical comparison of emetic incidence between experimental groups, and student's t-test was used for evaluating the difference in emetic latency.

2.3.3 Results.

2.3.3.1 General Behavior of the Cordotomized and the Vagotomized Cats. The only obvious neurological deficit resulting immediately from the dorsal cordotomy was a non-incapacitating locomotor ataxia. The cats postured normally for urination and defecation, and effectively avoided their excreta. They shivered normally during their emergence from anesthesia, responded normally to petting as with lifting of the back, groomed themselves in a normal fashion, and displayed no loss of appetite or outward disturbance in bowel function. In about two weeks, the cats regained their ability to jump from floor to benchtop and, for all practical purposes, they appeared indistinguishable from normal in their sheltered laboratory environment.

Cats subjected to subdiaphragmatic vagotomy showed no sign of abdominal discomfort and consumed food avidly upon recovery from anesthesia. The cats occasionally vomited spontaneously after wolfing a meal and so, for routine care, meals were given to them in divided portions. No remarkable difference in behavior was evident between cats vagotomized alone and those in which vagotomy was combined with cordotomy.

2.3.3.2 Effects of the Neurosurgical Interventions on Radioemetic Susceptibility. A dose-response relationship has been established in this laboratory for radiation-induced vomiting in normal cats under precisely the same conditions of exposure as presently employed for the operated animals (described above). The dose of 45 Gy was selected as being most consistent for baseline comparison of radioemetic susceptibility among experimental groups. The results are presented in table 3. In the group of normal animals, 11 of 12 (92%) vomited with an average latency to onset of 66 min after exclusion of one value (417 min) which is separated by about three standard deviations from the mean. In the solely cordotomized group, 5 of 8 cats vomited with an average latency of 146 min. The reduced emetic incidence is not significantly different from normal ($p= 0.11$) but the prolongation in latency is statistically significant from normal at $p< 0.001$. Two solely vagotomized cats failed to show any radioemetic protection except for an increased latency over normal ($p<.03$), and the vagotomy group was not further enlarged. Finally, all of three cats with combined cordotomy and vagotomy proved not to be susceptible to the emetic effect of irradiation, and as a group is significantly different from normal ($p<.001$). It should be added that among the five solely cordotomized cats that vomited, four responded with one emetic episode and the fifth with two episodes, whereas 8 out of the 11 normal cats vomited two or more times. This suggests that a blunting of radioemetic severity occurred in addition to the prolongation of latency observed as a result of the cordotomy alone.

Table 3. Acute emetic effect of 45 Gy ^{60}Co whole-body irradiation in normal, cordotomized, and vagotomized cats.

Condition	Cats tested	Cats vomited	Latency in min[a] Av. (Range)
Normal	12	11[b]	66 (3-129)[c,d]
Cordotomy	8	5	146 (119-185)[c]
Vagotomy	2	2	131 (123-138)[d]
Cord. & Vag.	3	0[b]	—

[a]From the end of radiation exposure (45 min at 1 Gy/min) to the first emetic episode.

[b]Groups are significantly different at $p=.001$.

[c]Groups are significantly different at $p<.001$ when "outlier" value (417 min) is excluded from the normal group.

[d]Groups are significantly different at $p<.03$ with the "outlier" value omitted from the normal group.

The single most important observation of a behavioral nature that emerged from this study is that all the cordotomized cats failed to become anorexic following their exposure to radiation, regardless whether they vomited or not. Most of them took a food treat immediately after having been irradiated. In all cases, they proceeded to eat their main meal upon presentation later in the day and consumed the entire amount before morning. This is in sharp contrast to the normal cats which in addition to vomiting after their irradiation invariably refused to eat the regular daily ration and left the food essentially untouched overnight. Also quite noteworthy, the cordotomized cats remained considerably more alert -- even playful -- by comparison with the normal group that generally became much subdued.

2.3.3.3 Histology of the Upper-Cord Lesions Sparing the AP. Specimen orientation in the microtome for making horizontal bulbospinal sections was arranged to provide a simultaneous slice through the AP with the widest part of the surgical lesion in the dorsal column nuclei. Two such sections from different animals are shown in figure 8 as examples of the variable width and symmetry in the surgical cuts. Of the 11 cats with upper-cord lesions, 6 specimens were sectioned in the horizontal plane and the remaining sectioned transversely. Figure 9 presents transverse sections of cordotomies from two cats, showing as well the intact area postrema above the level of the lesion in one cat (sections A and B). This cat was also vagotomized and was free of radiation sickness. The cat with the lesion shown in section C was not vagotomized and it vomited in response to irradiation but did not become anorexic.

Figures 8 and 9 are presented on pages 35 and 36, respectively.

It is evident from the figures that extensive damage was typically produced by the lesion-making operation in the gracile and cuneate nuclei, extending in some cases laterally into the spinal nucleus of the Vth cranial nerve. In no case was any damage apparent rostrally in the AP. Ventrally, the lesions reached down to the central canal, generally tapering to its base. The surgical intent was not to interrupt all dorsal column fibers, but only those passing through the dorsal column nuclei rostrally into the medulla. Undoubtedly, most ventrally decussating second-order neurons of those nuclei were spared caudal to the lesion thereby preserving a good measure of sensory function mediated by the spinal dorsal columns.

Figure 8. Histologic sections from two cordotomized cats taken in a horizontal plane passing through the area postrema, for comparison with the surface topography shown in figure 7. Both cats were also vagotomized and they manifested no signs of radiation sickness. No surgical damage is evident at the level of the area postrema. The sections were cut at a thickness of 20 μm, stained with luxol fast blue plus cresyl violet and photographed through a red filter.

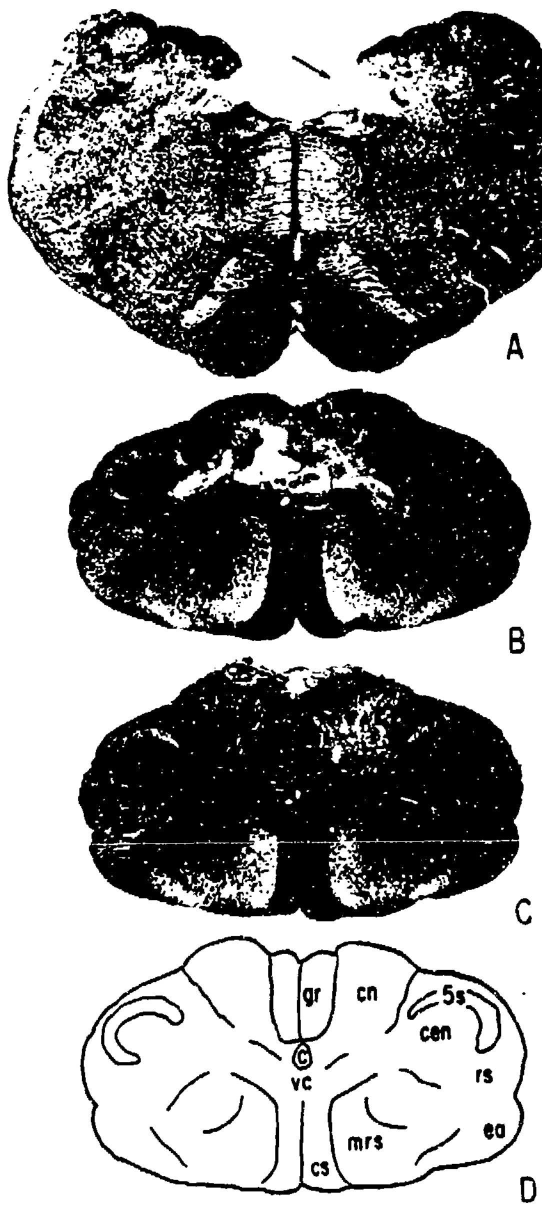

Figure 9. Transverse sections of high dorsal cordotomies in two cats (B and C). Section A (from the same specimen as B) passes through the medulla oblongata rostrally at the mid-level of the area postrema indicated by the arrow. The drawing (D) corresponds to the section immediately above showing the outlines of the intact dorsal columns for comparison with the lesion. Abbreviations are: gr-gracile nucleus; cn- cuneate nucleus; 5s-spinal trigeminal nucleus; cen-central nucleus of the dorsal horn; c-central canal; vc-ventral commissure; rs-rubrospinal tract; ea-external arcuate fibers; cs-corticospinal tract. Histological preparation as in figure 8.

2.3.4 Discussion.

Two decisive findings were made in this work on cats. First, radiation-induced vomiting was prevented selectively by high dorsal cordotomy combined with subdiaphragmatic vagotomy. Second, the cordotomy per se eliminated the anorexia and malaise of radiation sickness whether or not vomiting occurred in those cats with vagus nerves intact. Our present study thus confirms the original claim made by Borison (1957), but with a different means of interrupting the segmental afferent pathways, that the AP does not participate in the acute radiation sickness syndrome. These results obtained in cats stand in contrast to the initial work done on dogs by Chinn and Wang (1954) which implicated the emetic chemoreceptor trigger zone (i.e., the AP) as being essential for evoking acute radioemesis in that species. They suggested that an indirect humoral mechanism mediated the trigger zone activation. They did not at that time consider the possibility that peripheral afferent nerves might signal the response.

2.3.4.1 Role of the Vagal Afferent Nerve Fibers. Brizzee (1956) reported on the protective effect of ablating the area postrema against radiation-induced vomiting in the monkey. That work, however, was complicated by the observation that animals subjected to supradiaphragmatic vagotomy were perhaps better protected than their postremectomized counterparts. As a consequence, Brizzee left unanswered the question whether the responsible vagus nerve pathway led directly to the vomiting center or involved a link through the AP for inducing radioemesis. Three points deserve consideration in evaluating those results by comparison with the present study. (1) The monkey is approximately four times more sensitive to the emetic effect of radiation than is the cat. (2) The emetic response in the monkey was prevented without additional interruption of spinal afferent pathways. (3) The AP of the monkey is virtually non-functional as an emetic chemoreceptor trigger zone (Brizzee et al.,1955). In light of the present work, we believe that in the monkey and for the dose of radiation employed the vagus nerve serves as the necessary and sufficient afferent pathway from an abdominal source for the evocation of radiation-induced vomiting. Moreover, with the high risk of damage to the bulbar sensory vagal nuclei in the surgical procedure of postremectomy, a contributing afferent role of the AP as a synaptic link becomes an improbable mechanism operating in the radioemetic reflex arc. Conceivably, larger doses of radiation might recruit segmental afferent pathways along with the vagus nerve to evoke emesis in the monkey. Extrapolating from our present observations, if the dorsal column pathway serves generally to mediate the malaise of radiation sickness and if the monkeys described above experienced such malaise in the absence of vomiting, it follows that the spinal input was in fact activated subemetically in the evocation of the total radiation syndrome manifested in those animals.

Brizzee et al. (1958), from a follow-up study in dogs, concluded that the weight of evidence favored the area postrema as the central receptor site of action, presumably responsive to a humoral factor, or as the locus of an afferent pathway concerned with the radioemetic reflex. In contrast to the earlier work of Brizzee (1956) on monkeys, vagotomy was not performed in the dog as a peripheral control procedure. On the other hand, two dogs were protected against radioemesis by severe lesions made in the vagal nuclei situated subjacent to the area postrema. Brizzee et al. (1958) pointedly emphasized the need for total destruction of the area postrema in order to confer complete protection by this approach against x-irradiation emesis. As in the earlier work on monkeys, no attention was given in the dog study to a radioemetic influence possibly exercised through spinal afferent nerves.

Wang et al. (1958) reported an extensive series of experiments in dogs confirming their earlier work (Chinn and Wang, 1954) on the essential nature of the chemoreceptor trigger zone. The second work was also supposed to have dispensed with peripheral afferent sources as accountable for radiation sickness. The study of Wang et al. (1958) differed from those reported by Brizzee (1956) and Brizzee et al. (1958), in monkeys and in dogs, in the following respects. Wang et al. used a lower dose of radiation; their lesions of the central emetic trigger zone were not necessarily complete; and their operation of supradiaphragmatic vagotomy did not abolish the radioemetic effect. Nonetheless, the vagotomy performed by Wang et al. (1958) caused a significant prolongation, a doubling, in the onset latency of emesis which was not viewed as physiologically meaningful by the investigators. Further consideration is given below in detail to the effects of abdominal segmental denervations reported by Wang et al. (1958) as those relate to the present study.

In contrast to the work of Wang et al. (1958), Carpenter et al. (1986) reported no detectable effect of subdiaphragmatic vagotomy in 2 dogs on the vomiting after 8 Gy x-irradiation delivered over the region of the abdomen. The matter of proof for total vagotomy was not addressed. On the other hand, two postremectomized dogs failed to vomit within the allowed 4-hour period of observation following exposure to the same dose of radiation. Carpenter et al. (1986) concluded that radioemesis in the dog is humorally mediated at the area postrema by a substance apparently released from the stomach into the blood stream. The postrema lesions were described as including damage to surrounding structures, and the surgery as having resulted in a temporary state of "reduced motor coordination" presumably caused by cerebellar irritation. No surgical controls were mentioned. It is possible that dorsal column damage in the medulla could have contributed to the loss of coordination.

In our own work on cats reported herein added to that done by Borison (1957), neither supra- nor sub-diaphragmatic vagotomy, by itself, prevented radiation-induced vomiting but the denervation delayed the response. On the other hand, when the vagus nerves were spared in cats subjected to spinal deafferentation vomiting was evoked unpredictably from exposure to a normally effective dose of radiation. We were surprised to find no loss of appetite associated with the sporadic emesis occurring in cordotomized cats with intact vagus nerves. This observation suggests that separate routes exist in the visceral afferent pathways for messages affecting appetite and satiety, with impulses in the vagus apparently not affecting appetite after whole-body exposure to radiation.

We may conclude from the foregoing that as one part of a more general function in visceral regulatory behavior, the vagus nerves deliver to the vomiting center a fraction of the emesis provoking impulses arising from the abdomen in radiation sickness. In the monkey, the vagal fraction constitutes the sufficient stimulus; but this afferent source is only supplementary in dog and cat for producing the radioemetic effect.

2.3.4.2 Role of Co-sympathetic Visceral Afferent Nerves. We have demonstrated unequivocally that segmental afferent nerves constitute the primary reflex input for radiation sickness in cats. A relevant unanswered question is the extent to which co-sympathetic visceral afferent nerves contribute to that input. Borison (1957) could show no such contribution by performing chronic sympathetic ganglionectomy below T4 in two cats or by means of coeliac ganglionectomy in three additional cats, all combined with vagotomy. Wang et al. (1958) found no effect at all of "abdominal sympathectomy" performed as the sole procedure in dogs, but when combined with vagotomy it resulted in partial protection against the acute radioemetic response although this did not influence the delayed phase of vomiting. It is common neuroanatomical knowledge, that co-sympathetic visceral afferent nerve fibers enter the spinal cord as high as T4. In their early work assigning a contribution of such visceral afferents to the emesis induced by gastrointestinal irritation with CuSO4, Wang and Borison (1951) performed total sympathectomies in dogs. We therefore now find uninterpretable the results of "abdominal sympathectomy" in the experiments by Wang et al. (1958) who removed the sympathetic chains only from the ninth to sacral ganglia inclusive.

The available evidence as a whole thus indicates that the co-sympathetic visceral afferent nerve fibers do not serve as an obligatory pathway for radiation sickness but these possibly facilitate the evocation of radioemesis. At any rate, no light is shed upon the origin of such visceral sensory impulses. Nevertheless, it will be evident from the following part of the Discussion that the still unidentified abdominal source must be innervated primarily by extra-sympathetic segmental afferent fibers regardless whether it is also supplied by co-sympathetic afferents.

2.3.4.3 Role of the Dorsal Column Afferent Nerve Fibers. In originally seeking to reduce the radioemetic segmental field to its rostrocaudal limits, Borison (1957) found that spinal cord transection as low as T8 provided protection but that dorsal rhizotomy of T8-T10 did not. On the other hand, root section of T6-T10 proved to be effective whereas section of T4-T7 was not. The author then concluded that the distribution of afferents which mediate radiation-induced emesis is not restricted to two or three segments of the spinal cord but covers a segmental field that overlaps the splanchnic outflow. This is in accord with the varying and considerable superimposition of viscerotomes associated with parts of the stomach and upper intestine in the cat (McSwiney and Suffolk, 1938; Downman and Evans, 1957; Hazarika et al.,1964). It must be appreciated that prevention of radiation-induced vomiting by a regional neurotomy aimed at an unknown abdominal target of unknown size and performed in a small number of cats could well result from an incomplete denervation though sufficient to block the response. High dorsal column spinal cordotomy is of course even less discriminating with respect to the specific field of segmental origin. On the other hand, it provides a different dimension relating to the sensory modality that is involved. Downman and Evans (1957) point out that the splanchnic afferent pathways (i.e., co-sympathetic nerve fibers) are widely dispersed in the spinal cord with a concentrated ipsilateral representation in the dorsal funiculus and a scattered bilateral represention in the ventrolateral funiculus. Our high dorsal column section therefore resulted in the selective interruption of a distinct splanchnic population that could be involved in mediating radiation sickness.

Two additional points deserve emphasis, namely, (1) there appears to be no segregation of visceral and somatic afferent fibers in the dorsal columns of the cat; (2) the distribution of fibers in gracile and cuneate tracts do not conform to any strict laminar arrangement based on level of segmental origin (Yamamoto et al., 1956). Melzack and Bridges (1971) observed that cats with chronic lesions of the dorsal column nuclei performed motor activities better than did cats with more caudal lesions in the dorsal columns. Our cats with high cordotomy made through the dorsal column nuclei benefited from that advantage while best fulfilling the present neurosurgical strategy.

It has long been known that certain free nerve endings in the mesentery do not degenerate upon sympathetic and vagal interruption (Sheehan, 1933). Pacinian corpuscles in the mesentery are also of interest because they project along the dorsal column pathway (Amassian,1951). These are examples of various sensory elements that have yet to be scrutinized as the possible source(s) of radiation-induced emesis.

2.3.5 Conclusions.

We have demonstrated in the cat that acute radiation sickness was entirely prevented by high section of the spinal dorsal columns combined with interruption of the abdominal vagus nerves, procedures which spared the emetic function of the area postrema. The cordotomy alone thwarted the post-irradiation loss of appetite and development of malaise. It follows from these results, taken in conjunction with the lack of radioemetic protection afforded by postremectomy (Borison, 1957; Borison et al., 1987b), that the AP is not involved in the mechanism of radiation sickness in cats. The conflicting status of the AP as essential for radiation-induced vomiting in dogs and monkeys deserves re-evaluation in light of our newly identified major afferent neural pathway for the syndrome in the dorsal funiculus of the spinal cord.

SECTION 3

GENERAL CONCLUSIONS

The area postrema of the medulla oblongata, which contains the chemoreceptor trigger zone for vomiting, is not involved in the reflex mechanism of acute radiation-induced vomiting in cats. Therefore, no valid basis exists for the presumption that a chemical factor activates the area postrema in the acute phase of radiation sickness. By the exclusion of a chemosensory link in the radioemetic reflex arc, it follows that the emetic signal is neurally conducted all the way from its radiosensitive origin to the vomiting center.

Emetic refractoriness to radiation, observed at 24 hours after a prior supralethal exposure, is radioselective and does not involve any action at the area postrema. Since the central mechanism of vomiting is not disturbed on the day after exposure to a supralethal dose of radiation, it follows that the manifest resistance to a second exposure is developed at the radioemetic sensory source.

A major afferent pathway from the radioemetic sensory source to the vomiting center traverses the dorsal columns of the spinal cord. Interruption of this pathway at the dorsal column nuclei considerably ameliorated radiation sickness and it eliminated the attendant anorexia while leaving the area postrema undisturbed. The combination of subdiaphragmatic vagotomy with high dorsal cordotomy provided complete protection against acute radiation sickness. Hence, the reflex pathway of radiation sickness originates in the abdomen. The culpable radioemetic receptors are innervated by the vagus nerve and by spinal nerves that include essential extra-sympathetic afferent fibers. The precise abdominal origin of the emetic signal in acute radiation sickness remains to be established.

In light of the present observations in cats, it becomes necessary to examine the role of the spinal afferent pathway in all other species studied for a contribution of the area postrema to radiobiologic behavior.

SECTION 4

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